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Vitamin D and Brain Imaging in the Elderly: Should we Expect Some Lesions Specifically Related to Hypovitaminosis D?

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Abstract: Hypovitaminosis D is associated with cognitive decline in the elderly, but the issue of causality remains unresolved. Definitive evidence would include the visualization of brain lesions resulting from hypovitaminosis D. The aim of the present article is to determine, through a literature review, the location and nature of possible brain disorders in hypovitaminosis D. We found limited brain-imaging data, which reported ischemic infarcts and white matter hyperintensities in hypovitaminosis D, though did not provide their specific location or report any focal atrophy. Based on the finding of executive dysfunctions (i.e., mental shifting and information updating impairments) in the presence of hypovitaminosis D, we suggest that hypovitaminosis D is associated with a dysfunction of the frontal-subcortical neuronal circuits, particularly the dorsolateral circuit. Further imaging studies are required to corroborate this assumption and to determine whether hypovitaminosis D results in degenerative and / or vascular lesions.

Keywords: Vitamin D, brain mapping, cognition, older adults.

INTRODUCTION

Vitamin D is a secosteroid hormone and its deficiency has been associated with a variety of systemic diseases including brain dysfunction [1-10]. In particular, research studies during the past five years have repeatedly shown an association between hypovitaminosis D and both global and domain-specific declines in cognitive performance [4]. The strength of these associations is yet limited by the cross-sectional design of the studies, which prevents determining whether dementia precipitates hypovitaminosis D or whether hypovitaminosis D has a role in precipitating cognitive decline and dementia. Definitive evidence to infer causality would be to visualize an impact of hypovitaminosis D on the brain, for example to highlight some brain variation specifically related to hypovitaminosis D. In particular, several brain structures may be affected by low levels of vitamin D since this neurosteroid hormone has been experimentally shown to have anti-neurodegenerative as well as anti-ischemic effects, by binding to the neuronal Vitamin D Receptors (VDR) [1-3]. Determining which part of the brain varies in the presence of hypovitaminosis D, and by which mechanism, therefore seems crucial. We wished to underline in this manuscript new prospects in the understanding of vitamin D action in the brain. In particular, our aim was to determine from the literature the location and nature of possible brain lesions in older adults with hypovitaminosis D.

METHODS

In general, the location of a brain lesion can be investigated in two ways: either it can be located by paraclinical techniques, including morphological and functional brain imaging or electroencephalography; or it is the result of a clinical reflection based on the interpretation of the neurological signs, which are usually closely linked to the strategic location of the damage. To be as comprehensive as possible, we examined all references to vitamin D in the brain-imaging and clinical literatures.

RESULTS

First, we found that the literature of brain imaging has yielded only one study on this specific issue [5]. In this study, the authors did not find a significant association between vitamin D status and hippocampal volume among a cohort of 318 older community-dwelling subjects (mean age 73.5±8.1 years, 72.6% women). However, it was found that ischemic infarcts (16.1% *versus* 6.9%, $P<0.01$) and white matter hyperintensities (higher volume: 4.9 *versus* 2.9 mL, $P=0.004$; and higher grade: 3.2 *versus* 2.2, $P=0.02$) were associated with hypovitaminosis D [5]. Nevertheless, this study did not specify the location of the vascular lesions and did not seek other focal atrophies.

Second, the analysis of the literature on clinical signs of hypovitaminosis D helped to identify brain areas of interest. More precisely, previous studies found significant associations between serum 25-hydroxyvitamin D concentrations (25OHD) and scores on domain-specific cognitive tests assessing executive functions. Executive functions refer to a heterogeneous set of high-level processes that control and

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regulate other abilities and behaviours [11]. More precisely, executive functions can be grouped into three specific areas: mental shifting (i.e., the ability to move from one cognitive operation to another), cognitive inhibition (i.e., the ability to inhibit an automatic response), and information updating (i.e., updating information in working memory) [11]. Each subdomain of executive functions can be tested separately with specific psychometric measures, and a possible link between vitamin D level and each sub-test score can be explored. In particular, Buell *et al.*, [7] found among 1,080 older adults (75 years; 76% female) that serum 25OHD concentration was associated with better mental shifting performance illustrated by lower score on the part B of the Trail Making Test (TMT B) ($\beta = -0.73$ with $P=0.02$) after adjustment for age, gender, body mass index, education level, kidney function, level of physical activity, alcohol consumption, center and season tested. A longitudinal cohort study by Llewellyn *et al.*, [8] confirmed the link between vitamin D and mental shifting by showing among 858 adults aged 65 and older, followed over 6 years, the relative risk for significant decline in TMT B score was 1.31 [95% CI: 1.03-1.51] among subjects initially deficient in vitamin D compared to those with a normal vitamin D status, even after adjustment for age, gender, education level, initial TMT B score, alcohol and tobacco consumption, depression, energy intake, rate of vitamin E, degree of mobility and season tested. Parallel, an association was also found between low levels of vitamin D and impaired updating performance assessed with a task of spatial working memory [9]. In this study, the authors examined 387 European aged 55 to 87 years (49.4% female). The results showed that the serum 25OHD concentration was inversely correlated with the total number of errors in the task ($r = -0.174$, $P < 0.003$) [8]. In addition, subjects belonging to the highest tertile of 25OHD made fewer errors than those in the lowest tertile of 25OHD ($P = 0.04$) [8]. Finally, Jorde *et al.*, [10] explored the association between vitamin D and cognitive inhibition using the Stroop test in 148 adults aged 62 years on average (46% female). In this study, the authors failed to find a significant association between serum 25OHD concentrations and the Stroop test score Parts 1 and 2 ($\beta = 0.12$ with $t = 1.05$) or Part 3 ($\beta = -0.07$ with $t = -0.68$) after adjustment for age, gender, body mass index, education level, health status and serum parathyroid hormone concentration [9].

DISCUSSION

The identification of the impact of hypovitaminosis D on the brain through the use of imaging techniques has received little attention to date. The limited available data reported more ischemic infarcts and white matter hyperintensities in the presence of hypovitaminosis D, but did not provide the location of these vascular lesions and reported no focal atrophies. In contrast, a growing body of neuropsychological research has demonstrated impairments in executive functions, particularly in mental shifting and information updating, among adults with hypovitaminosis D [7-10]. Since the expression of a neurological injury is directly related to its location, the detailed analysis of the neuropsychological signs observed in hypovitaminosis D should help to identify brain areas of interest to evaluate in future studies.

Anatomically, executive functions are primarily underpinned by the frontal lobes, but subcortical structures are also involved. At the cortical level, the prefrontal cortex is the structure devoted to executive functions and is the only cortical region capable of integrating memory and motivational, emotional and somatosensory information towards achieving a single action [12-14]. At the subcortical level, the caudate nucleus, the putamen, the pallidum, the nucleus accumbens and the thalamus are connected to the frontal cortex by three main frontal-subcortical neuronal circuits: the dorsolateral, orbitofrontal and anterior cingulate circuits. Because of the brain structures specifically involved in these circuits, each circuit is responsible for specific subdomains of executive functions [12-19]. In particular, the dorsolateral circuit - which is supplied by the middle cerebral artery - is involved in the selection of goal, planning, mental shifting, information updating, working memory, visual spatial memory and self-activation [12,14-16], while the orbitofrontal circuit, vascularized by anterior and middle cerebral arteries, is involved in social behavior and cognitive inhibition [12,17,18]. Finally, the anterior cingulate circuit - supplied by the anterior cerebral artery - is involved in error correction, behavior monitoring and cognitive inhibition [12,14, 19]. Any lesion in these frontal-subcortical circuits, independent of its level (i.e. cortical or sub-cortical) or nature (i.e., atrophy or vascular), may result in domain-specific executive dysfunctions [12-19]. As a consequence, the finding of executive dysfunctions primarily characterized by impairments of mental shifting and information updating in hypovitaminosis D [7-10] makes us suggest that hypovitaminosis D could be associated with a dysfunction of the frontal-subcortical neuronal circuits, particularly the dorsolateral circuit. Underlying lesions would be either degenerative with cortical and / or subcortical atrophies in the circuit, or ischemia that would preferentially affect the vascular territory of the middle cerebral artery. Further imaging studies are therefore needed to corroborate these hypotheses, to determine whether the dorsolateral circuit is specifically altered in the case of hypovitaminosis D, and whether hypovitaminosis D may contribute to degenerative or vascular lesions.

Such a finding would help to better understand the involvement of vitamin D in the course of dementia, and would also provide an additional rationale for prescribing vitamin D supplementation among adults with hypovitaminosis D.

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Authors' Contribution

- Annweiler takes responsibility for the integrity of the work as a whole, from inception to published article.
- All authors meet all of the following criteria: (1) contributing to the conception and design, or analyzing and interpreting data; (2) drafting the article or revising it critically for important intellectual content; and (3) approving the final version to be published.

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- The sponsors had no role in the design and conduct of the study, in the collection, management, analysis, and interpretation of the data, or in the preparation, review, or approval of the manuscript.

CONFLICT OF INTEREST

- Dr. Annweiler: serves as an unpaid consultant for Ipsen Pharma company. He has no relevant financial interest in this manuscript.
- Prof. Montero-Odasso: reports no conflicts of interest. He has no relevant financial interest in this manuscript.
- Dr. Muir: reports no conflicts of interest. She has no relevant financial interest in this manuscript.
- Prof. Beauchet: serves as a consultant for Ipsen Pharma company. He has no relevant financial interest in this manuscript.

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